REMARKS

Claims 10-36 are pending in the application. Claims 10-24 have been withdrawn from consideration by the Office Action as being directed to non-elected subject matter. Claims 25-32 have been examined. Claims 33-36 have been added. The claims as presented contain six (6) independent claims. Five independent claims were originally filed, therefore, the fee of $210.00 under 37 C.F.R. § 1.16(h) (large entity) for one extra independent claim is enclosed herewith.

Claim 25 has been amended to recite that the disclosed three-dimensional coordinates of the HPTPbeta catalytic domain [SEQ ID NO:7], as set forth in Figures 202-252, are employed to determine the binding mode of a compound, to determine if other compounds have similar binding modes and to subsequently assay whether the compounds have HPTPbeta activity. Support for this amendment can be found at page 9, line 20 to page 13, line 8 and the claims as originally filed.

Claim 26 has been amended to recite that the disclosed three-dimensional coordinates of the HPTPbeta catalytic domain [SEQ ID NO:7], as set forth in Figures 7-102, are employed to determine the binding mode of a compound, to determine if other compounds have similar binding modes and to subsequently assay whether the compounds have HPTPbeta activity. Support for this amendment can be found at page 9, line 20 to page 13, line 8 and the claims as originally filed.

Claims 33-36 have been added. Support for these claims can be found in the specification at page 6, line 19 – page 8, line 23.

By these amendments no new matter has been added.

REJECTION UNDER 35 U.S.C. § 103(a)

The Office Action has rejected Claims 25-32 under 35 U.S.C. § 103(a), as allegedly obvious over Cohen *et al.* "Molecular Modeling Software and Methods for Medicinal Chemistry" *J. Med. Chem.* (1990), 33(3), pp. 883-889 (hereinafter "Cohen") in view of Fachinger *et al.* "Functional interaction of vascular endothelial-protein-tyrosine phosphatase with the Angiopoietin receptor Tie-2" *Oncogene* (1999), Vol. 18, pp. 1189-1198 (hereinafter "Fachinger") and further in view of ***In re Gulack* 217 USPQ 401 (Fed. Cir. 1983)** and ***In re Ngai* 70 USPQ2d 1862 (Fed. Cir. 2004)**. The Office Action's rejection is respectfully traversed.

The Office Action's rejections dated June 12, 2007 have been maintained. That Office Action states "Cohen *et al.* [discloses] the commercial availability of computers and various package software used for imaging and identifying potential drugs using atomic coordinates of biological molecules." The Office Action further states "[a]tomic coordinates can not render a known method for identifying inhibitors of enzymes novel or non-obvious." The Office Action cites ***In re Gulack*** as finding that non-functional descriptive material cannot render a claim non-obvious.

As it relates to the finding of ***In re Gulack***, the court found that Gulack's descriptive material was essential to the invention. The same situation applies to the disclosed atomic coordinates; without the X-ray data, the 3-Dimensional structure of the HPTPbeta molecule could not be displayed. The display allows the medicinal chemist to select which amino acids to include into the binding site. As indicated by Cohen in the citation discussed herein below, X-ray coordinate and crystallographic data are essential for determining which atoms potentially comprise the binding sites. Knowing the 3-Dimentsional structure thus allows a potentially active compound to be tested by the chemist for the proper docking in the binding sites of the HPTPbeta molecule.

Cohen adumbrates the techniques useful for assisting medicinal chemists in displaying the complex three dimensional structure of a macromolecule. Thus, modeling programs are an important tool that allows the researcher to think through and visualize the problem (in this instance, determining which compounds will dock at the binding pockets of HPTPbeta) and find a drug candidate that mediates an angiogenesis related disorder. As such, a computer program can be powerful in assisting the chemist in performing rational drug design.

Cohen states at page 891, column 1, lines 36-43:

> A realistic appraisal of the current state of the art is represented by Cohen et al.'s ambitions prediction of the core tertiary structure of Interleukin-2 ***prior to its determination by X-ray crystallography***; while the prediction had several key features correct, it was too inaccurate to be useful for drug design – even small errors in the placement of secondary and tertiary structure can lead to major errors in the complete model. (Emphasis added.)

Cohen therefore uses his own findings as an example to suggest that modeling programs *per se* cannot provide an accurate prediction of a complex molecule without the necessary X-ray crystallographic coordinates. Therefore, the Office Action's assertion that the atomic

coordinates are nonfunctional descriptive material is incorrect. Using these coordinates to provide a 3-Dimensional display is in many instances the first step in rational drug design using modeling programs. Cohen teaches at page 891, column 2, lines 4-11:

> Drug-receptor "docking" is typically done ***interactively*** with molecular surface displays (e.g. "extra radius" surface) used to guide the fit, based on hydrophobic or electrostatic potential color coding. Since it is difficult to hit a moving target, the binding site is usually treated as completely rigid initially, while ***the conformation of the ligand is adjusted interactively***. (Emphasis added.)

As such, modeling programs simply provide a template with which the chemist can interact. The options open to the researcher are only limited by his or her ability to think or to recognize proper from improper molecular conformations. For example, Cohen discloses at page 891, column 2, last paragraph:

> Multiple binding modes are often possible, as shown by the X-ray structure of an elastase-product complex in which the ligand is bound backwards to the established mode of productive binding. It can be very difficult with interactive methods to find the most likely binding mode candidates.

While the modeling program can display the 3-Dimensional coordinates of a biologically active molecule, it is the chemist who ultimately must use creativity and judgment to obtain the correct results. Cohen summarizes this fact at page 893, column 1, lines 7-12:

> All of the approaches we have described so far are analytical and oriented toward modeling known structures. Where do the structures of novel candidate drugs come from? Actual molecular structure design is still a formidable challenge dependent on the creativity, ingenuity, and experience of the medicinal chemist.

Therefore, the disclosure of Cohen supports the fact that modeling programs are useful tools for rational drug design, but that it is the intuition and cognitive ability of the medicinal chemist that determines which compounds are drug candidates that are to be tested for their activity. In addition, X-ray crystallographic coordinates would not be considered to be non-functional descriptive material as alleged by the Office Action. Instead, they are critical to being able to construct a 3-dimensional model of HPTPbeta and, thus, to delineate the structure of the HPTPbeta catalytic domain. As such, the disclosure of Cohen does not suggest that a modeling program could select which molecules would interact with a biologically active molecule, nor

does Cohen suggest that a modeling program would be able to select which atoms comprise the catalytic domain of HPTPbeta. Cohen does teach, however, that by first acquiring X-ray crystallographic coordinates, a computer modeling program can assist the medicinal chemist in using his or her creativity, ingenuity, and experience to design a drug candidate.

The Office Action further states that Fachinger discloses "HPTPbeta is the human analog of VE-PTP and suggested that the human [enzyme has] the same function [as] VE-PTP in regulating Tie-2." This citation is a reiteration of that which Applicants have recited at page 1, lines 13-14, "HPTPbeta (Kruegar et al. EMBO J., 9, (1990) has been suggested *inter alia* for modulating the activity of angiopoietin receptor-type tyrosine kinase TIE-2."

The Fachinger disclosure relates to an "analysis of the *in vivo* expression of VE-PTP mRNA by *in situ* hybridization to frozen sections of mouse embryonic tissues" in that "[s]trong hybridization signals were visible in endothelial cells forming blood vessels, whereas no specific signals were detected in blood cells or smooth muscle cells surrounding the vessels." (*See* the second paragraph of page 5948.) As such, the Fachinger disclosure is absent any teaching or suggestion relating to a method for identifying a drug compound for the treatment of an angiogenesis mediated disorder or that a method for identifying a drug compound for the treatment of an angiogenesis mediated disorder is desirable.

The Office Action has failed to establish a case of obviousness by asserting a combination of the teachings of Cohen and Fachinger. Cohen does nothing more than establish the fact that molecular modeling exists *per se* and that through the use of such modeling programs, the ingenuity of the medicinal chemist can be applied to determining which compounds are likely drug candidates. Therefore, Cohen establishes nothing more than what the artisan already knows; computer programs are tools used in drug design, but that functional information, such as X-ray crystallographic data, are necessary for elucidating which compounds are suitable for testing as a drug candidate. Fachinger does not suggest finding a substrate for HPTPbeta in order to affect angiogenesis. Fachinger does not suggest obtaining X-ray crystallographic coordinates for use in determining which atoms of which amino acids comprise the active sites of HPTPbeta. Instead, Fachinger concludes "[f]uture studies toward the identification of potential ligands of VE-PTP will help to clarify its biological activity." Thus Fachinger does not disclose that modulation of VE-TPT activity, and hence the activity of its

human homologue, HPTPbeta, would lead to a basis for treating an angiogenesis mediated disorder.

Applicants respectfully request reconsideration and withdrawal of the rejection of Claims 25-32 under 35 U.S.C. § 103(a).

CONCLUSION

The Examiner is invited and encouraged to directly contact the undersigned if such contact may enhance the efficient prosecution of this application to issue.

A Credit Card Payment Form PTO-2038 authorizing payment in the amount of $210.00, which includes the fee under 37 C.F.R. § 1.16(h) (large entity) for one extra independent claim is enclosed. This amount is believed to be correct; however, the Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment, to Deposit Account No. 14-0629.

Respectfully submitted,

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CERTIFICATE OF ELECTRONIC TRANSMISSION UNDER 37 C.F.R. § 1.8			
I hereby certify that this correspondence, including any items indicated as attached or included, is being transmitted via electronic transmission via EFS-Web on the date indicated below.			
Name of Person Signing (Print/Type)	Richard S. Echler		
Signature	/ Richard S. Echler/	Date	September 16, 2008